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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 31

Application Number: 08/323060
Filing Date: 10/14/94
Appellant(s): Philip C. Comp

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 8/7/96..

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of the invention contained in the brief is deficient because of the following reasons. Regarding appellants statements on page 3, first paragraph of the Appeal Brief filed 8/7/96, the claimed compositions do not have a component wherein the first component is an "inhibitor of one or more natural anticoagulants". Claim 14 states that the first component is "an inhibitor of a natural anticoagulant", not "one or more natural anticoagulants". Regarding appellants statements on page 3, second paragraph of the Appeal Brief filed 8/7/96, the claimed method is not "based on the administration of an inhibitor of greater than 90% of one or more natural anticoagulants". Claim 1 states the method uses a compound "to prevent anticoagulation by greater than 90% of activated protein C in human plasma wherein the compound is an inhibitor of an anticoagulant".

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 1-9,11-16 and 19-21 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

Appellant's brief includes a statement that claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,202,253	Esmon et al.	4/13/93
5,130,244	Nishimaki et al.	7/14/92

Furie et al., Cell, vol. 53, 1988, pages 505-518.

No new prior art has been applied in this examiner's answer.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

The Fass declaration filed 4/11/96 has been considered in view of the fact that a signed copy of said declaration has been submitted. In view of the Fass declaration filed 4/11/96, the rejection under U.S.C. § 112 first paragraph as enunciated in paragraph 17 of the Office Action mailed 11/27/95 is withdrawn. However, the rejections under U.S.C. § 112 first paragraph as enunciated in paragraphs 20 and 21 of the Office Action mailed 11/27/95 are maintained as they would apply to the use of the instant inventions in humans. The rejections under U.S.C. § 112 first paragraph as enunciated in paragraphs 20 and 21 of the Office Action mailed 11/27/95 have been incorporated into one rejection.

The rejection of claims 1-9,11-13,19-21 under U.S.C. § 112 first and second paragraphs as enunciated in paragraph 25 of the Office Action is withdrawn because it essentially deals with enablement issues that are dealt with in other pending rejections.

Rejections Under 35 U.S.C. § 112, First Paragraph

(1) Claims 1-9,11-16,19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the HPC-4 antibody to inhibit microvascular bleeding when said antibody is given systemically prior to bleeding, does not reasonably provide enablement for the claimed methods and compositions. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody has unique properties which distinguish it from other antiprotein C antibodies, including CA^2+ dependency (see column 2, last paragraph). It is not apparent or predictable that any antibody per se against protein C would be able to mediate the microvascular bleeding inhibition effect achieved when this antibody with unique properties is used. In addition it is equally unclear whether nonantibody agents that inhibit protein C function would be able to mediate the effect seen using the HPC-4 antibody. In the specification it is recited that the agent used must inhibit, "greater than 90% of potential activated protein C in human plasma" (see specification, page 14, third paragraph). It is not disclosed in the specification whether other agents can achieve this degree of protein C inactivation as occurs with the unique HPC-4 antibody. Esmon et al. (US Patent 5,202,253) teach that the HPC-4 antibody can prevent the activation of protein C, but does not bind to protein C once it is activated (see column 2, last paragraph). It is therefore unpredictable as to whether the HPC-4 antibody can be used to prevent microvascular bleeding after the bleeding has already occurred, because activated protein C is now present and the HPC-4 antibody does not bind to protein C once it is activated. There is no experimental evidence disclosed in the specification indicating that the HPC-4 antibody can be used to treat microvascular bleeding when the antibody is administered after microvascular bleeding has occurred. All of the experiments described in the specification

administered the HPC-4 antibody prior to the initiation of bleeding. With regards to the use of inhibitors of an anticoagulant other than the HPC-4 anti-protein C antibody, the specification discloses that, "the possibility of pathologic thrombosis must certainly be considered whenever a systemic thrombogenic drug is utilized"(page 14, last paragraph). While the specification provides evidence that this does not occur in the pig model when HPC-4 anti-protein C antibody is used, there is no disclosure in the specification as to whether other inhibitors of an anticoagulant encompassed by the claims would cause pathologic thrombosis when administered in vivo (even in the pig model), thus precluding the use of said agents in vivo in humans.

(2) Claims 4 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification has provided insufficient guidance with respect to the topical administration of an inhibitor of a natural anticoagulant of the instant invention. There is no guidance in the specification as to dosage or particular time when the inhibitor of an anticoagulant would be administered topically. It is also unclear as to whether topical administration will result in the absorption of sufficient quantities of the instant invention to achieve sufficient inhibition of protein C that is constantly arriving at the site of microvascular

bleeding via influx of blood. Esmon et al. (US Patent 5,202,253) teach that the HPC-4 antibody can prevent the activation of protein C, but does not bind to protein C once it is activated (see column 2, last paragraph). It is unclear as to whether the administration of said antibody when administered topically to a bleeding site where activated protein C is present would have any effect on microvascular bleeding. Activated protein C is innately present at the site of bleeding because it is involved in the mechanism whereby bleeding occurs. No working examples (eg. actual experimental data) are disclosed in the specification indicating that an inhibitor of a natural anticoagulant of the instant invention can actually be used topically and have any effect on microvascular bleeding. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.

(3) Claims 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma which secretes the antibody known as HPC-4 is required to practice the instant invention as recited in claim 21 which recites the respective antibody. As a required element, the hybridoma and cell line must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If

said hybridoma and cell line are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the instant hybridoma. See 37 CFR 1.802.

The specification does not provide a repeatable method for obtaining the hybridoma which secrets the antibody known as HPC-4. There is no disclosure in the specification of the particular epitope recognized by the antibody produced by said hybridoma and therefore a routineer would not be able to produce said hybridoma based on the disclosure of the specification. Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody has unique properties which distinguish it from other antiprotein C antibodies, including $CA^{2}+$ dependency (see column 2, last paragraph). There is no disclosure in the specification as to how such an antibody would be made. In addition, the claim reads on a specific deposited hybridoma that would have specific properties of the particular clone or subclone that was deposited at the time of deposit. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. 112.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.801-1.809 for additional explanation of these requirements.

While the aforementioned hybridoma has been deposited with the ATCC, appellants need to comply with all of the deposit requirements as per 37 CFR 1.801-1.809. Appellant needs to submit a statement with regards to the HPC-4 producing hybridoma indicating that, "All restrictions imposed by the depositor on the availability to the public of the deposited

material will be irrevocably removed upon the granting of the US patent." (see 37 CFR 1.808). There is no indication that the HPC-4 producing hybridoma was deposited under conditions of the Budapest treaty, therefore applicants need to meet all requirements specified in 37 CFR 1.801-1.809 for cell lines not deposited under conditions of the Budapest treaty.

Rejections Under 35 U.S.C. § 112, First and second Paragraphs

Claims 14-16 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite in that it is unclear as to whether the composition consists of two physically separate agents or two agents that are physically mixed together. A composition is by definition a physical mixture of ingredients. Thus, appellants use of the term composition in claim 14 is repugnant to its art recognized use because claim 14 recites that one component is suitable for systemic administration, while the second component is suitable for topical administration and therefore the ingredients are not physically mixed. If the language used is interpreted as including two agents mixed together, than there is no disclosure in the specification of such a composition. This interpretation is supported by claim 14 which recites that one component is suitable for systemic administration, while the second component is

suitable for topical administration. The specification (page 14, second paragraph) teaches that an inhibitor of a natural anticoagulant, when prepared for systemic administration is prepared with a liquid pharmaceutical carrier such as saline or phosphate buffered saline. The specification teaches that topically prepared agents are administered in powdered or lyophilized (freeze dried powder) form. Obviously, these two forms could not coexist in the same physical preparation. Furthermore, a composition containing thrombin could not be injected systemically due to the art known complications that arise from systemic injection of thrombin (eg. massive internal coagulation). Therefore the specification is not enabling for the instant invention.

Rejections Under 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(1) Claims 1-3,7,11-13,20,21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Esmon et al. (US Patent 5,202,253).

The claims are drawn to a method for inhibiting microvascular bleeding in a patient by blocking greater than 90% of activated protein C function in human plasma by treatment with a compound that is an inhibitor of an anticoagulant.

Esmon et al (US Patent 5,202,253) teaches the HPC-4 antiprotein C antibody(see entire document). Esmon et al. (US Patent 5,202,253) teaches that said antiprotein C antibody can be used to promote clotting (eg. inhibit bleeding) (see paragraph four, column 12). This antibody is an inhibitor of the anticoagulant protein C (see Abstract). Esmon et al. teaches the HPC-4 antibody in a pharmaceutically acceptable carrier, at a dosage to block greater than 90% of endogenous protein C (see column 13, paragraph 4). By blocking greater than 90% of endogenous protein C, the antibody blocks the generation of greater than 90% of activated protein C in plasma, because protein C is present in the plasma in an inactive state which is then activated, and this activation step is prevented by the HPC-4 antibody (see Abstract), therefore blocking greater than 90% of activated protein C in human plasma. Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed (see paragraph three, column 13). Esmon et al. (US Patent 5,202,253) teach a pharmaceutical composition of the instant antibody (see paragraph four, column 13). A routineer would have realized that since the antiprotein C antibody can be used to promote clotting, including clotting of the microvascular bed of a tumor, then the instant antibody could be used to promote microvascular clotting in any application that was desired.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed the method of the instant invention because Esmon et al teaches the HPC-4 antiprotein C antibody and the use of said antibody to promote clotting, Esmon et al. teaches the HPC-4 antibody in a pharmaceutically acceptable carrier, at a dosage to block greater than 90% of endogenous protein C , Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed (see paragraph three, column 13) and a routineer would have realized that since the antiprotein C antibody can be used to promote clotting, including clotting of the microvascular bed of a tumor, then the instant antibody could be used to promote microvascular clotting in any application that was desired. Burns, skin grafting and cerebral contusions are art known situations in which microvascular bleeding occurs (see specification, page 1). Esmon et al. teach that the pharmaceutical composition of the instant antibody was administered systemically(see paragraph four, column 13).

One of ordinary skill in the art would have been motivated to do the aforementioned to treat microvascular bleeding in disease states, in view of the teachings of Esmon et al. (US Patent 5,202,253) that the instant antibody can be used to promote clotting including clotting of the microvasculararature. One of ordinary skill in the art would have a reasonable expectation of success because the use of anti-protein C antibody to promote clotting, including clotting of the microvasculararature was known in the art.

(2) Claims 4 and 18 are rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) as applied to claims 1-3,7,11-13 above, and further in view of Nishimaki et al. (US Patent 5,130,244).

The claims are drawn to the method of the instant invention where the inhibitor of an anticoagulant is administered topically.

The previous rejection under 35 U.S.C. § 103 in this Examiners Answer makes obvious the instant invention, except for topical administration of the inhibitor of an anticoagulant. Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery (see column 1, second paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed the method of the instant invention where the inhibitor of an anticoagulant is administered topically because the previous rejection under 35 U.S.C. § 103 makes obvious the instant invention, except for topical administration of the inhibitor of an anticoagulant and Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery. One of ordinary skill in the art would have been motivated to do so because Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery.

(3) Claims 5,6,8,9,14-16 and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) as applied to claims 1-3,7,11-13 above and Esmon et al. (US Patent 5,202,253) in view of Nishimaki et al. (US Patent 5,130,244) as applied to claims 4 and 18 above, and further in view of Furie et al.

The claims are drawn to a method for inhibiting microvascular bleeding in a patient by blocking greater than 90% of activated protein C function with a compound that is an inhibitor of an anticoagulant in combination with administering a coagulant topically at the site of bleeding. The coagulant is administered topically, while the inhibitor of an anticoagulant is administered systemically or topically. The claims are also drawn to a composition containing an inhibitor of an anticoagulant in combination with a coagulant. The composition is interpreted as including two physically distinct agents, eg. an agent for intravenous administration and a separate agent for topical administration, in so far as this is the form of the instant invention disclosed in the specification.

The previous rejections under 35 U.S.C. § 103 in this Examiners Answer makes obvious the method for inhibiting microvascular bleeding in a patient by blocking greater than 90% of activated protein C function with a compound that is an inhibitor of an anticoagulant (eg. antiprotein C antibody) and wherein said inhibitor is administered systemically. The previous rejections under 35 U.S.C. § 103 make obvious the topical administration of said inhibitor of an anticoagulant. Neither rejection makes obvious the use of a topical coagulant in addition to the use of the inhibitor of an anticoagulant.

Nishimaki et al. teach that thrombin (a coagulant) is used clinically as a topical agent to exert a blood coagulating effect (see column 1, paragraph 2). It would have been obvious to a routineer that thrombin could have used as a coagulant to treat any known form of bleeding, including microvascular bleeding. Furie et al. teach that clot formation (eg. clotting or coagulation) is mediated by thrombin via the effect of thrombin on fibrinogen (see page 505, column one, last paragraph, continued on column two). Furie et al. also teach that thrombin can also lead to the activation of protein C, which is an anticoagulant which would prevent blood clotting (see page 506, column two, last paragraph, continued on page 507). In a physiological setting, these two effects of thrombin interact to determine how much clotting occurs when thrombin is present at a site of bleeding. In view of the fact that the clotting ability of thrombin is negatively regulated by protein C, it would have been obvious to a routineer, that the administration of antiprotein C antibody would increase the clotting ability of thrombin, via elimination of the generation of protein C, which is a anticoagulant which counteracts the coagulant property of thrombin.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed inventions because the previous rejections under 35 U.S.C. § 103 makes obvious the method for inhibiting microvascular bleeding in a patient by blocking greater than 90% of activated protein C function with a compound that is an inhibitor of an anticoagulant (eg. antiprotein C antibody) and wherein said inhibitor is administered systemically, the previous rejections under 35 U.S.C. § 103 makes obvious the

topical administration of said inhibitor of an anticoagulant, Nishimaki et al. teach that thrombin (a coagulant) is used clinically as a topical agent to exert a blood coagulating effect and Furie et al. disclose that the clotting ability of thrombin is negatively regulated by protein C, and it would have been therefore obvious to a routineer, that the administration of antiprotein C antibody would increase the clotting ability of thrombin, via elimination of the generation of protein C, which is an anticoagulant which counteracts the coagulant property of thrombin. A routineer would have administered the antiprotein C antibody either systemically or topically depending on the particular form of microvascular bleeding that was being treated. Based on the aforementioned, it would have been obvious to a routineer to create a pharmaceutical composition consisting of an inhibitor of an anticoagulant(antiprotein c antibody) in a form for systemic use (or topical use) in combination with a coagulant (thrombin) for topical use. Nishimaki et al. teach thrombin in a dosage of between approximately 1000 and 10,000 units (see column 1, fourth paragraph from the bottom).

One of ordinary skill in the art would have been motivated to do the aforementioned in order to increase the efficacy of thrombin to inhibit microvascular bleeding, in view of the teaching of Furie et al. that protein C was an anticoagulant generated by thrombin which negatively regulated the coagulation caused by thrombin, and the knowledge that antiprotein C antibody could inhibit anticoagulation mediated by protein C.

This examiner's answer does not contain any new ground of rejection.

11) Response to argument

Rejections Under 35 U.S.C. § 112, First Paragraph

(1) Claims 1-9,11-16,19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of the HPC-4 antibody to inhibit microvascular bleeding when said antibody is given systemically prior to bleeding, does not reasonably provide enablement for the claimed methods and compositions. Appellants arguments have been considered and deemed not persuasive. Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody has unique properties which distinguish it from other antiprotein C antibodies, including CA^2+ dependency (see columns 2-4). Esmon et al. (US Patent 5,202,253) teaches that the HPC-4 antibody is distinguishable over other antiprotein C antibodies in that it binds a unique epitope, has CA^2+ dependency and binds protein C, but not activated protein C. It is not apparent (or predictable) that any antibody per se against protein C would be able to mediate the microvascular bleeding inhibition effect achieved when the aforementioned HPC-4 antibody with unique properties is used because Esmon et al. establish that the HPC-4 antibody has characteristics not seen in other art known antiprotein C antibodies. In addition, it is equally unpredictable whether nonantibody agents that inhibit

protein C function would be able to mediate the effect seen using the HPC-4 antibody. In the specification it is recited that the agent used must inhibit, "greater than 90% of potential activated protein C in human plasma" (see specification, page 14, third paragraph). It is not disclosed in the specification whether other agents can achieve this degree of protein C inactivation as occurs with the unique HPC-4 antibody. Appellant has not responded to these issues in the instant Appeal Brief. Regarding appellants comments on page 18 of the instant Appeal Brief, appellant has not responded to the aforementioned issues in the instant appeal Brief. It is unpredictable as to whether the HPC-4 antibody can be used to prevent microvascular bleeding after the bleeding has already occurred, because activated protein C is now present and the HPC-4 antibody does not bind to protein C once it is activated. Esmon et al. (US Patent 5,202,253) teach that the HPC-4 antibody can prevent the activation of protein C, but does not bind to protein C once it is activated (see column 2, last paragraph). There is no disclosure in the specification as to the efficacy of the instant antibody in treating microvascular bleeding when the antibody is administered after microvascular bleeding has occurred. All of the experiments described in the specification administered the HPC-4 antibody prior to the initiation of bleeding. Regarding appellants comments on page 8, last paragraph, continued on page 9 of the instant Appeal Brief, there is no evidence of record to support said comments. Furthermore, said comments fail to address the issue of how the HPC-4 antibody can have any effect on activated protein C, when said antibody does not bind to activated protein C. In view of the fact that all of the experiments using HPC-4 were

performed wherein said antibody was administered prior to the induction of bleeding and said antibody does not bind activated protein C (eg. found where bleeding occurs) it is not predictable in the absence of further experimental evidence as to whether HPC-4 would have any effect on bleeding when it was administered after bleeding had already started. Regarding appellants comments on page 8, penultimate paragraph, last sentence, of the instant Appeal Brief, the experiments disclosed in the specification disclose the use of HPC-4 antibody given prior to the start of microvascular bleeding. With regards to the use of inhibitors of an anticoagulant other than the HPC-4 anti-protein C antibody, the specification discloses that, "the possibility of pathologic thrombosis must certainly be considered whenever a systemic thrombogenic drug is utilized"(page 14, last paragraph). Regarding appellants comments on page 9, first complete paragraph of the instant Appeal Brief, the specification discloses that, "the possibility of pathologic thrombosis must certainly be considered whenever a systemic thrombogenic drug is utilized"(page 14, last paragraph). While the specification provides evidence that this does not occur in the pig model when HPC-4 anti-protein C antibody is used, there is no disclosure in the specification as to whether other inhibitors of an anticoagulant encompassed by the claims would cause pathologic thrombosis when administered in vivo (even in the pig model), thus precluding the use of said agents in vivo in humans. Furthermore, the quotation from the specification (page 14, last paragraph) clearly applies to the experiments that were disclosed in the specification. Regarding appellants comments on page 10 of the instant Appeal Brief, there is no evidence of record that any

compound other than HPC-4 antibody can inhibit microvascular bleeding or "prevent anticoagulation by greater than 90% of activated protein c in human plasma" (as per claim 1). The Taylor et al., 1991 reference does not show that antibodies against an anticoagulant have any effect on microvascular bleeding or that an antibody against a natural anticoagulant can "prevent anticoagulation by greater than 90% of activated protein C in human plasma". In fact, the Taylor et al. reference deals with the host response to *E. Coli* infusion and concludes that whatever response is seen in said model is related to the interaction of protein C or S and cytokine responses (see page 362, second column, last two paragraphs) and is independent of the interaction of protein S or C in coagulation. Regarding the Fass declaration, said declaration does not discuss the specific issues under consideration in this rejection. In addition, there is no evidence supplied in said declaration that Fass has any expertise in the area of antibodies or the effect of antibodies on coagulation. Regarding various comments in the Fass declaration about various legal issues (what is enabled by the instant application, etc.), there is no evidence of record that Fass has any expertise or training in patent law such that his determination about patentability need be given any weight.

(2) Claims 4 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. Appellants arguments have been considered and deemed not persuasive.

The specification has provided insufficient guidance with respect to the topical administration of an inhibitor of a natural anticoagulant of the instant invention. There is no guidance in the specification as to dosage or particular time when the inhibitor of an anticoagulant would be administered topically. It is also unclear as to whether topical administration will result in the absorption of sufficient quantities of the instant invention to achieve sufficient inhibition of protein C that is constantly arriving at the site of microvascular bleeding via influx of blood. Esmon et al. (US Patent 5,202,253) teach that the HPC-4 antibody can prevent the activation of protein C, but does not bind to protein C once it is activated (see column 2, last paragraph). It is unclear as to whether the administration of said antibody when administered topically to a bleeding site where activated protein C is present would have any effect on microvascular bleeding. Activated protein C is innately present at the site of bleeding because it is involved in the mechanism whereby bleeding occurs. No working examples (eg. actual experimental data) are disclosed in the specification indicating that an inhibitor of a natural anticoagulant of the instant invention can actually be used topically and have any effect on microvascular bleeding. Appellant has not addressed these issues in the instant Appeal Brief. Regarding appellants comments on page 8, penultimate paragraph, last sentence, the examples in the specification (pages 17 to 21) do not disclose experiments where

an inhibitor of an anticoagulant is used topically. The Fass declaration does not address the issues under consideration in this rejection.

(3) Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Appellants arguments have been considered and deemed not persuasive.

It is apparent that the hybridoma which secretes the antibody known as HPC-4 is required to practice the instant invention as recited in claim 21 which recites the respective antibody. As a required element, the hybridoma and cell line must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If said hybridoma and cell line are not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the instant hybridoma as per 37 CFR 1.801-1.809.

Regarding appellants reference to In re Argoudelis on page 15 of the instant Appeal Brief, said case refers to a US patent application wherein a biological material had been deposited by an applicant. The issue under consideration was the sufficiency of the deposit (eg. whether it was necessary that the deposited material be publicly available at the time of filing), not whether a material deposited in a second unrelated US patent would suffice to meet the appropriate deposit requirements as now required under 37 CFR 1.801-1.809. The quote from

In re Argoudelis that appellant cites on page 15 of the instant Appeal Brief refers to the sufficiency of the conditions of deposit of the deposit in the US application under consideration in said case. The paragraph in In re Argoudelis (page 1394, first column) that follows that quote from In re Argoudelis that appellant cites on page 15 of the instant Appeal Brief indicates that the deposit in the application under consideration in said case was sufficient to meet the requirements as they apply to the application in which they were deposited, not that the deposited material was therefore enabled when cited in a unrelated patent. Therefore the findings in In re Argoudelis are not relevant to the issue under consideration. Appellant has not deposited the hybridoma producing the HPC-4 antibody in compliance with 37 CFR 1.801-1.809. Appellants have not met the deposit requirements under 37 CFR 1.808 or 37 CFR 1.806. Furthermore, regarding 37 CFR 1.806, because the hybridoma producing the HPC-4 antibody was deposited with the ATCC in 1988 (see specification, page 12) , even if the deposit was made under conditions satisfying all the deposit requirements in the US patent in which said deposit would made, said cell line would not be publicly available for the period of enforceability of any US patent issued from the US patent application currently under consideration (see M.P.E.P. (Rev. 1, Sept. 1995) section 2408, page 2400-13, first column, first complete paragraph).

Rejections Under 35 U.S.C. § 112, First and second Paragraphs

Claims 14-16 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Appellants arguments have been considered and deemed not persuasive.

Claim 14 is indefinite in that it is unclear as to whether the composition consists of two physically separate agents or two agents that are physically mixed together. A composition is by definition a physical mixture of ingredients. Thus, applicants use of the term composition in claim 14 is repugnant to its art recognized use because claim 14 recites that one component is suitable for systemic administration, while the second component is suitable for topical administration and therefore the ingredients are not physically mixed. If the language used is interpreted as including two agents mixed together, than there is no disclosure in the specification of such a composition. This interpretation is supported by claim 14 which recites that one component is suitable for systemic administration, while the second component is suitable for topical administration. The specification (page 14, second paragraph) teaches that an inhibitor of a natural anticoagulant, when prepared for systemic administration is prepared with a liquid pharmaceutical carrier such as saline or phosphate buffered saline. The specification teaches that topically prepared agents are administered in powdered or lyophilized (freeze dried powder) form. Obviously, these two forms could not coexist in the same physical preparation. Furthermore, a composition containing thrombin could not be injected

systemically due to the art known complications that arise from systemic injection of thrombin (eg. massive internal coagulation). Therefore the specification is not enabling for the instant invention.

Rejections Under 35 U.S.C. § 103

(1) Claims 1-3,7,11-13,20,21 are rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253). Appellants arguments have been considered and deemed not persuasive.

Regarding appellants arguments on pages 20-22 of the instant Appeal Brief, Esmon et al (US Patent 5,202,253) teaches the HPC-4 antiprotein C antibody(see entire document). Esmon et al. (US Patent 5,202,253) teaches that antiprotein C antibody can be used to promote clotting (eg. inhibit bleeding) (see paragraph four, column 12). Regarding appellants comments that Esmon et al. teach that antibody against protein C is useful for "normalization of bleeding", no such quote is actually to be found in Esmon et al. Esmon et al. (US Patent 5,202,253) teaches antiprotein C antibody can be used to promote clotting (eg. inhibit bleeding) (see paragraph four, column 12). The promotion of clotting is the mechanism wherein bleeding is stopped. Therefore, it would have been obvious that antiprotein C antibody can be used to stop bleeding. Regarding appellants comments on page 20, last paragraph of the instant Appeal Brief, there is no limitation in the claims under consideration

that indicates that the inhibitor of protein C need be as effective as thrombin or tissue thromboplastin. Furthermore, the only inhibitor which the specification discloses is as effective as thrombin or tissue thromboplastin is HPC-4 antibody given prior to the initiation of bleeding as per the experiments disclosed in pages 17-21 of the specification. Regarding appellants comments on page 21, first five sentences of the instant Appeal Brief, the HPC-4 antibody binds inactive protein C. Inactive protein C is found throughout the body. Therefore, said antibody would not be expected to have any effect until bleeding actually occurred locally (eg. during the time period during which protein C undergoes activation). Furthermore, Esmon et al. (US Patent 5,202,253) teaches that said antiprotein C antibody can be used to promote clotting (eg. inhibit bleeding) (see paragraph four, column 12). Regarding appellants comments on page 21, paragraph two of the instant Appeal Brief, the synergy which appellant discloses is only seen with HPC-4 antibody and the topical use of thrombin. The specification discloses that such synergy does not occur with thromboplastin and HPC-4 (page 20 of the specification, lines 20-21). Based on this selective response, it is unclear as to whether the synergy seen with HPC-4 and thrombin would occur with other antibodies and thrombin. Furthermore, there is no disclosure in the specification of other antibodies and topical coagulants that lead to the degree of synergy seen in experiments using HPC-4 and thrombin. There are currently no claims under consideration that specifically recite the use of HPC-4 and thrombin, so that this synergism is irrelevant to the claims that are actually under consideration. Regarding appellants comments on page 23, first incomplete paragraph of the

instant Appeal Brief, Esmon et al. (US Patent 5,202,253) teaches that said antiprotein C antibody can be used to promote clotting (eg. inhibit bleeding) (see paragraph four, column 12).

(2) Claims 4 and 18 are rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) as applied to claims 1-3,7,11-13 above, and further in view of Nishimaki et al. (US Patent 5,130,244).

Regarding appellants comments about Mishimaki et al. on page 21 of the instant Appeal Brief, said comments are irrelevant to the claims under consideration because there are no claims under consideration that read on the systemic administration of a coagulant. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed the method of the instant invention where the inhibitor of an anticoagulant is administered topically because Esmon et al. makes obvious the instant invention, except for topical administration of the inhibitor of an anticoagulant and Nishimaki et al. teach that it was known in the art that an agent which exerted a blood coagulating effect could be applied topically for use as a hemostatic agent in surgery.

(3) Claims 5,6,8,9,14-16 and 19 are rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) as applied to claims 1-3,7,11-13 above and Esmon et al. (US Patent 5,202,253) in view of Nishimaki et al. (US Patent 5,130,244) as applied to

claims 4 and 18 above, and further in view of Furie et al. Appellants arguments have been considered and deemed not persuasive.

Regarding appellants comments on page 22 of the instant Appeal Brief, Furie et al. teach that clot formation (eg. clotting or coagulation) is mediated by thrombin via the effect of thrombin on fibrinogen (see page 505, column one, last paragraph, continued on column two). Furie et al. also teach that thrombin can also lead to the activation of protein C, which is an anticoagulant which would prevent blood clotting (see page 506, column two, last paragraph, continued on page 507). In a physiological setting, these two effects of thrombin interact to determine how much clotting occurs when thrombin is present at a site of bleeding. In view of the fact that the clotting ability of thrombin is negatively regulated by protein C, it would have been obvious to a routineer, that the administration of antiprotein C antibody would increase the clotting ability of thrombin, via elimination of the generation of protein C, which is a anticoagulant which counteracts the coagulant property of thrombin. Regarding appellants comments on page 22 of the instant Appeal Brief, paragraph three, Esmon et al. (US Patent 5,202,253) teaches that antiprotein C antibody can be used to promote clotting (eg. inhibit bleeding) (see paragraph four, column 12). Regarding motivation to produce the composition of claims 14-16, Esmon et al. (US Patent 5,202,253) teaches that antiprotein C antibody can be used to promote clotting and Nishimaki et al. teach that thrombin (a coagulant) is used clinically as a topical agent to exert a blood coagulating effect (see column 1, paragraph 2). Furie et al. teach that clot formation (eg. clotting or coagulation) is mediated by thrombin via

the effect of thrombin on fibrinogen (see page 505, column one, last paragraph, continued on column two). Furie et al. also teach that thrombin can also lead to the activation of protein C, which is an anticoagulant which would prevent blood clotting (see page 506, column two, last paragraph, continued on page 507). In a physiological setting, these two effects of thrombin interact to determine how much clotting occurs when thrombin is present at a site of bleeding. In view of the fact that the clotting ability of thrombin is negatively regulated by protein C, it would have been obvious to a routineer, that the administration of antiprotein C antibody would increase the clotting ability of thrombin, via elimination of the generation of protein C, which is a anticoagulant which counteracts the coagulant property of thrombin and therefore it would have been advantageous to use thrombin in combination with HPC-4 antibody. Regarding appellants comments on page 22 of the instant Appeal Brief, no reference of record has been provided which teaches away from the claimed invention. Regarding the Fass declaration, it is unclear wherein said declaration teaches that the prior art teaches away from the claimed invention. Regarding the Fass discourse on obviousness in page 5 of the Fass declaration, no weight has been given to Fass's opinion about obviousness because he has no legal training or expertise in the area of patent law.

(12) For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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